

Risk factors for ocular surface damage in Mexican patients with dry eye disease: a population-based study

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Purpose: To analyze potential risk factors for ocular surface damage in a representative population of Mexican patients with dry eye disease (DED).

Patients and methods: A prospective and cross-sectional population-based epidemiologic cohort study was conducted through a survey of patients with symptoms, signs, known pre-existing diagnosis, and clinical conditions related to DED. Fluorescein staining, tear break-up time (TBUT), and Oxford lissamine green staining were performed on both eyes of patients enrolled in the study.

Results: A total of 2,725 surveys including 1,543 (56.6%) women and 1,182 (43.3%) men were analyzed. Most common pre-existing diagnosis included dry eye (58%), chronic blepharitis (17%), and ocular allergy (15%). More than 70% of patients had a positive fluorescein test, and this prevalence increased proportionally to the number of reasons for consultation. The same was true for gender ($P < 0.001$) and age ($P < 0.0001$), with women showing a strong correlation with age ($R^2 = 0.93912$, $P = 0.001$). The association between positive fluorescein staining and diagnosis was significant for dry eye ($P < 0.0001$), Sjögren's syndrome ($P < 0.0001$), and glaucoma ($P < 0.05$). No significant association between TBUT and age or gender was found, but the shorter the TBUT, the larger the prevalence of fluorescein staining. Reduced TBUT was seen more frequently in patients with dry eye (57%), ocular allergy (16%), and chronic blepharitis (15%). Most patients (39%) with Oxford grades III and IV were older, complained of red eye (51.0%), foreign body sensation (47.0%), burning (46.0%), and were using eye drops (67%) and systemic medications (47%).

Conclusion: The Mexican profile of patients with significant ocular surface damage related to DED includes women at older ages, complaining of red eye, foreign body, and burning sensation. Diagnoses of dry eye, Sjögren's syndrome, and glaucoma were also risk factors for significant ocular surface damage, along with long-term use of preserved eyes drops and systemic medications.

Keywords: ocular surface disease, lacrimal dysfunction, tear break-up time, fluorescein staining, Oxford scale

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Introduction

Dry eye disease (DED) represents a significant burden of public health with a prevalence higher than many systemic severe disorders like diabetes mellitus and heart disease.¹⁻³ Multiple studies have demonstrated that DED symptoms have a significant impact on patient's vision-related quality of life.⁴⁻⁶ Severe DED symptoms and signs have been correlated with difficulties in physical, social, and mental functioning, limiting the patient's capacity to perform daily tasks such as watching TV, reading, driving,

and carrying out their work, as well as inducing anxiety and depression.^{5,7,8}

Epidemiologic studies have shown that the prevalence of dry eye symptoms with or without signs ranges from 5% to 50%, whereas when only signs are considered for diagnosis, the prevalence rates are generally higher, reaching up to 75% in certain populations.^{9,10} Many different factors influence the wide variation in DED frequency, including geographic, climate, and demographic aspects, but equally important is the lack of clear standardization of disease definition and classification nomenclature.^{9,11–13}

DED has been recently redefined by the Dry Eye Disease Workshop (DEWS-2017) as “a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.”¹⁴ Ocular inflammation and damage to the ocular surface, particularly the corneal and conjunctival epithelium, are the common denominators of the disease.^{15,16}

The purpose of the present report is to analyze the prevalence of risk factors for ocular surface damage related to DED in a population-representative cohort from Mexico.

Patients and methods

This is a prospective and cross-sectional population-based epidemiologic cohort study. A survey was designed to evaluate the risk factors for ocular surface damage related to DED in the general population. The study was performed by a representative number of ophthalmologists from large cities of Mexico on all eligible patients visiting their clinics in a single given week. All patients who volunteered to participate in the study read and signed an informed consent approved by the Ethics and Research Committee of the GRoup of Evaluation on Conservatives in Ophthalmology (El GRECO) and the study complied with the tenets of the Declaration of Helsinki.

The survey was only applied to patients who had a pre-existing diagnosis related to DED or whenever symptoms and signs associated with diminished production or increased evaporation of tears were present. Demographic data and reason for consultation, consisting of red eye, burning, ocular pain, foreign body sensation, and blurred vision, were cumulatively collected from every patient. A selection of pre-existing diagnosis and ocular conditions related to dry eye was used to identify patients with potential ocular surface damage through specific close-ended and open questions. If the interviewer recorded one or more of these conditions,

then a clinical evaluation of ocular surface damage including fluorescein staining, tear break-up time (TBUT), and the Oxford lissamine green staining scheme was performed in both patient’s eyes.^{17,18} All ophthalmologists who participated in the study received specific instructions of how the ocular surface evaluation should be performed to standardize the clinical parameters measured.

Only complete survey forms were included for analysis. Data obtained from every patient were collected in Excel spreadsheets (Windows® version, 2017, Windows update 4011165 for Microsoft Excel 2017; Microsoft Corporation, Redmond, WA, USA) and analyzed using *R*-Statistics version 3.4.3 for Windows (GNU-Free Software Foundation, Boston, MA, USA). Different types of statistical analysis were applied: descriptive statistics was performed to demographic variables (media, standard deviation, and range). Graphic analysis (bars, distribution pies, and frequency histograms) was also performed. Finally, the calculation of the estimations and contrasts of hypothesis was based on the distribution of comparative proportions using the chi-squared test for discrete variables and the Student’s *t*-test for comparison of mean differences of unequal variances. All hypothesis contrasts were considered significant with a *P*-value <0.05 and with a reliability of 95%. The risk factor for ocular surface damage related to DED was obtained by a multivariate logistic regression model using the presence of DED as the dependent variable.

Results

Fifty-five ophthalmologists from ten different states randomly distributed all over the country performed a dry eye poll among the eligible patients. The majority of patients surveyed (90.6%) lived in seven of the most inhabited cities of the country: Mexico City, Guadalajara, Monterrey, Puebla, Leon, Toluca, and Aguascalientes (Table 1). More than half of the population included for study lives at very high altitude: Mexico City (2,240 m above sea level), Toluca (2,605 m), and Puebla (2,147 m). Only the cities of Veracruz and Ensenada are located at sea level. The geographic, climate, and environmental characteristics of these cities are presented in Table 1.

Almost one-third of the patients analyzed (31.0%) worked at offices spending most of their time reading and using digital screens. The other two-thirds of the patients worked part-time in the office or at stores and mostly outside in a great variety of jobs like city workers, drivers, sellers, construction, etc.

From a total of 3,014 interviews performed within a 4-month period, only 2,725 complete surveys were considered for analysis. The population studied comprised

Table 1 Geographic and environmental characteristics of the cities inhabited by most of the patients included in the survey

City	Population INEGI-2015 no. of habitants	Altitude m (ft)	Temperature range, Celsius (°F)	Relative humidity (%)	Level of contamination 2018 (PM ₁₀)	Patients surveyed, no. (%)
Mexico City	8,918,653	2,240 (7,349)	10–25 (50–77)	56.6	42	1,042 (38.2)
Guadalajara	4,930,537	1,546 (5,072)	12–28 (53–82)	61	41	473 (17.3)
Monterrey	4,437,643	540 (1,771)	4–38 (39–100)	64.4	86	508 (18.6)
Puebla	2,393,604	2,147 (7,004)	7–23 (44–73)	20	32	162 (5.9)
Leon	1,967,501	1,815 (5,954)	7–31 (44–88)	57.2	58	57 (2.0)
Toluca	1,747,712	2,605 (8,546)	1–24 (34–75)	64	80	192 (7.0)
Aguascalientes	1,044,049	1,888 (6,194)	3–32 (37–89)	40	24	44 (1.6)
Veracruz	891,805	10 (32)	21–30 (70–86)	80	13	217 (7.9)
Ensenada	486,639	16 (52)	10–30 (50–86)	81	NA	30 (1.1)

Abbreviations: °F, Fahrenheit; INEGI, Instituto Nacional de Estadística y Geografía (National Institute of Statistics and Geography); NA, not available; PM₁₀, particulate matter-10 µm.

1,543 (56.6%) women and 1,182 (43.3%) men with an age range distribution as given in Table 2.

The most common pre-existing diagnosis recorded was dry eye in 1,717 (63.0%) patients, followed by chronic blepharitis in 489 (17.9%) patients, and ocular allergy in 457 (16.7%) patients (Table 3).

A total of 1,135 (41.6%) patients were already on topical treatment with at least one unspecified eye drop, and 572 (20.9%) patients were on at least one systemic medication at the time the survey was applied. Also, one-third of patients (31.0%) referred to use an electronic device with a digital screen (desk-top, lap-top, tablet, or cell phone) on a daily basis (Table 3).

When comparing the proportion of patients with a positive corneal fluorescein staining and the pre-existing diagnosis, there was a significant association with the diagnosis of dry eye ($P=0.0001$), Sjögren's syndrome ($P=0.0001$), and glaucoma ($P=0.04$). Patients with Sjögren's syndrome had a 1.34 (OR, 95% CI=1.27–1.42) higher risk for developing ocular surface damage, while the risk factor was 1.33 (OR, 95% CI=1.26–1.41) for patients with dry eye and 1.19 (OR, 95% CI=1.12–1.26) for patients with glaucoma (Figure 1).

Table 2 Distribution of the population studied according to gender and age range

Age range (years)	No. of men (%)	No. of women (%)	Total (%)
<25	295 (24.9)	228 (14.7)	523 (19.1)
25–45	228 (19.2)	470 (30.4)	698 (25.6)
46–65	437 (36.9)	388 (25.1)	825 (30.27)
>65	222 (18.7)	457 (29.6)	679 (24.9)
Total	1,182 (43.3)	1,543 (56.6)	2,725 (100)

Around one-third of all respondents complained of typical dry eye symptoms including red eye, burning, foreign body sensation, and blurred vision (Figure 2). Of all patients who experienced at least one dry eye-related symptom, $\geq 70\%$ had a positive fluorescein test with similar proportions according to symptomatology for all patients analyzed (Figure 2).

Moreover, the prevalence of a positive corneal fluorescein staining increased proportionally to the number of reasons for consultation recorded for each patient, from 66% with one reason to 92% with ≥ 4 reasons, being statistically significant

Table 3 Prevalence of pre-existing ocular and systemic diagnosis, and clinical conditions related to dry eye disease

Ocular disease	No. of patients (%) (N=2,725)
Dry eye	1,717 (63.0)
Chronic blepharitis	489 (17.9)
Ocular allergy	457 (16.7)
Previous ocular surgery ^a	395 (14.4)
Glaucoma	288 (10.5)
Contact lens wear	247 (9.0)
Facial paralysis	48 (1.7)
Herpes Zoster ophthalmicus	23 (0.8)
Systemic disease	
Diabetes mellitus	287 (10.5)
Sjögren's syndrome	105 (3.8)
Rosacea	95 (3.4)
Autoimmune diseases (RA/SLE)	62 (2.2)
Other conditions	
Topical eye drops	1,135 (41.6)
Digital screen use	845 (31.0)
Systemic medication	572 (20.9)

Note: ^aKeratorefractive and cataract surgery.

Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

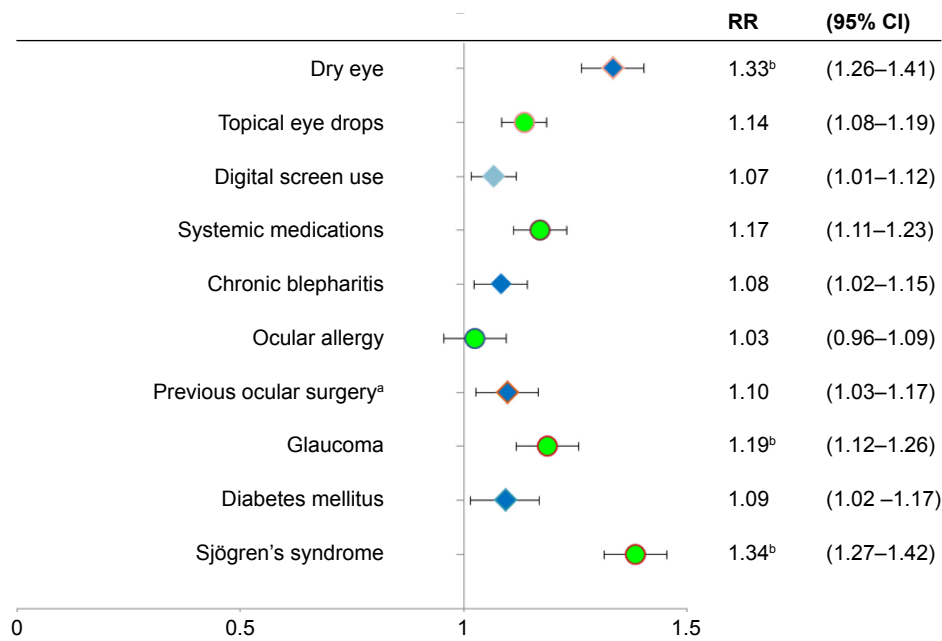


Figure 1 Forest plot showing the relative risk (chi-squared test) for ocular surface damage recorded as positive corneal fluorescein staining in at least one eye according to pre-existing diagnosis and clinical conditions.
Note: ^aKeratorefractive or cataract; ^b $P < 0.05$.
Abbreviation: RR, risk ratio.

for patients with four ($P=0.036$) and more than four reasons for consultation ($P < 0.009$) (Figure 3).

The same was true for both gender ($P < 0.001$) and age ($P < 0.0001$) as shown in Figure 4. Of note was the increased proportion of women who showed a positive fluorescein staining with age ($R^2=0.93912$, $P=0.001$).

Regarding TBUT, no significant association was found between reduced TBUT and age or gender in our population,

but the shorter the TBUT, the larger the prevalence of corneal fluorescein staining. This association was also true for higher Oxford Scale scores (Figure 5).

Around 29% of patients complaining of typical dry eye symptoms like red eye, foreign body sensation, pain, burning, and blurred vision also had shorter TBUTs (< 10 seconds). On the other hand, larger proportions of reduced TBUT were recorded for patients with a pre-existing

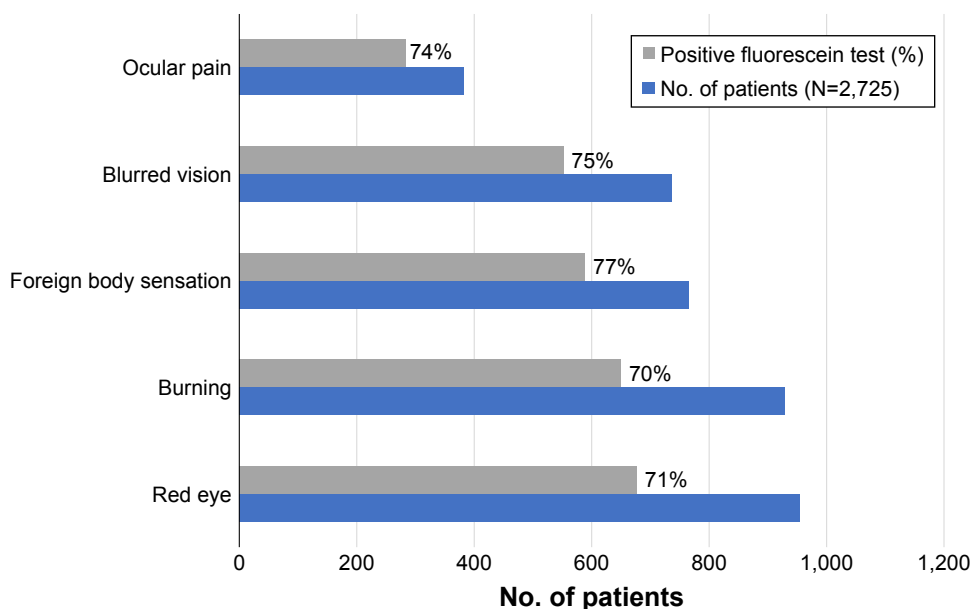


Figure 2 Prevalence of dry eye symptoms and its correlation with a positive fluorescein test in at least one eye.

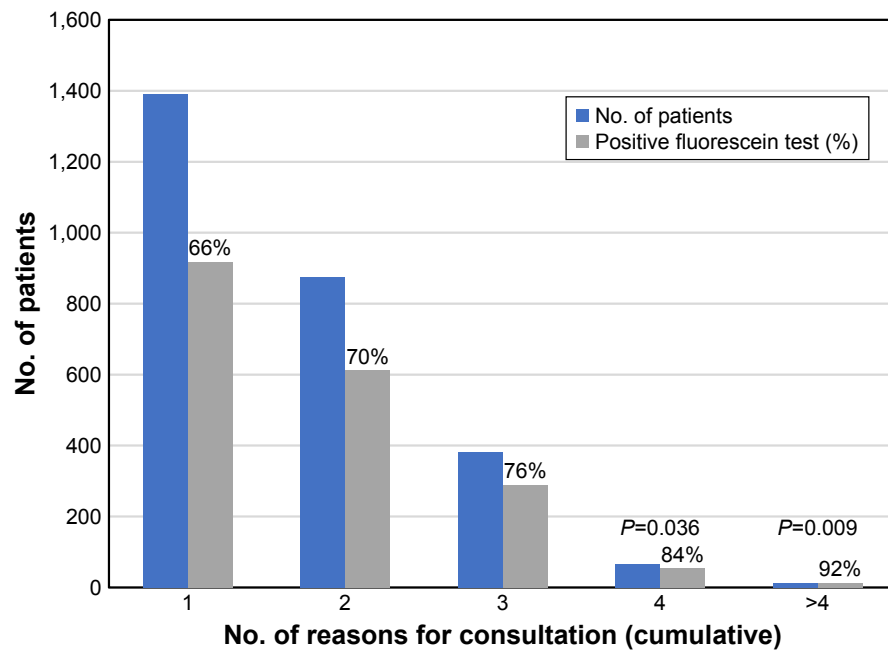


Figure 3 Proportion of a positive fluorescein test according to the number of reasons for consultation.

diagnosis of dry eye (57%), ocular allergy (16%), and chronic blepharitis (15%).

The distribution of patients with ocular surface damage according to the Oxford score is presented in Table 4.

The largest proportion of patients (45.0%) had grade I staining, while 22.0% of them had grade II staining. The great majority of patients with grades III and IV in the Oxford scale were women (64%), and most of these patients (39%)

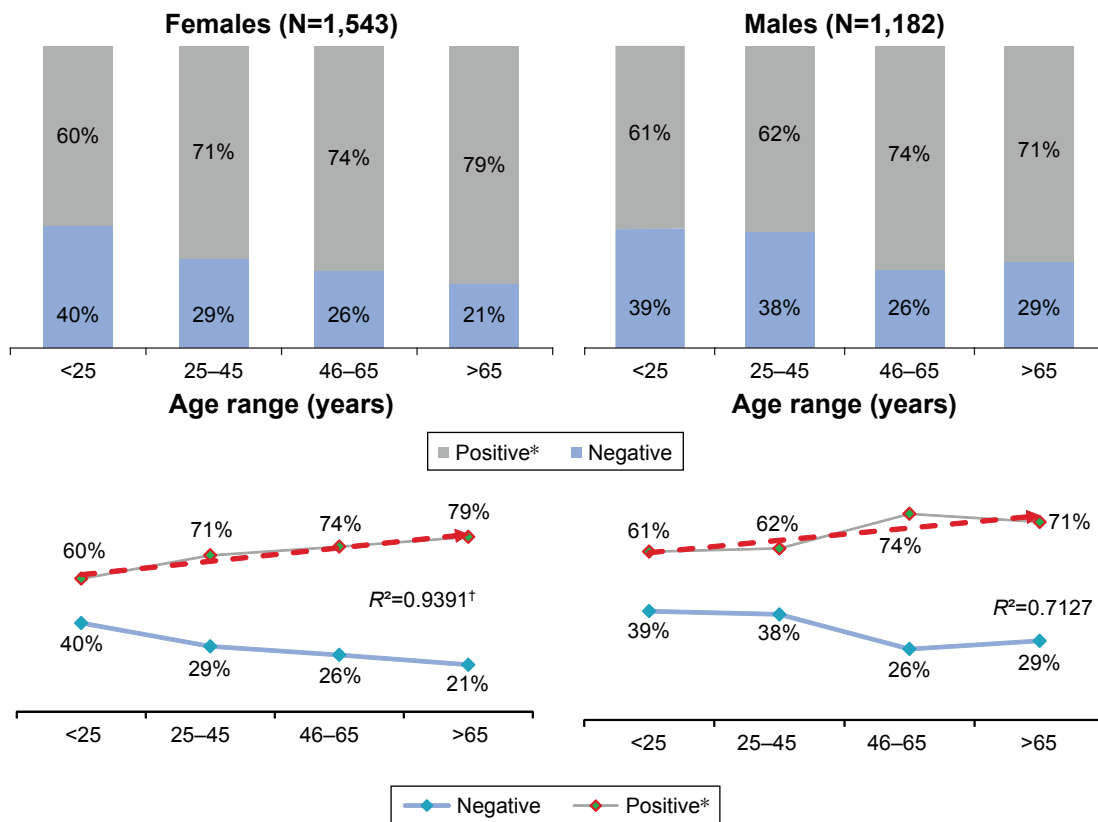


Figure 4 Proportions of a positive fluorescein test according to gender and its correlation with age.
Notes: *Positive fluorescein test in at least one eye. †(P=0.001)

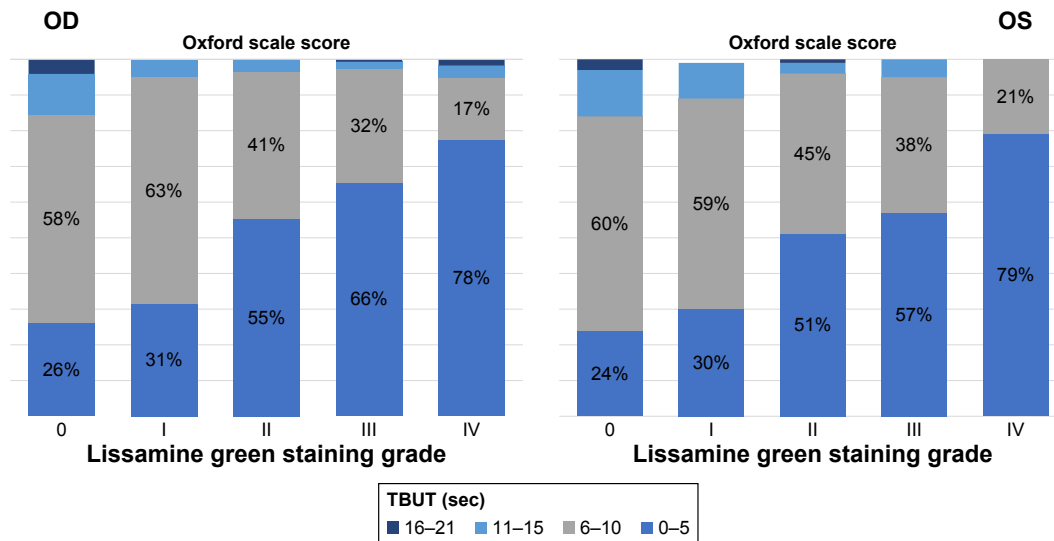


Figure 5 Proportions of lissamine green staining scores for each eye according to the Oxford scheme and its relation to the tear break-up time. **Abbreviations:** TBUT, tear break-up time; sec, seconds; OD, right eye; OS, left eye.

belonged to the oldest age group (>65 years old) and complained of red eye (51.0%), foreign body sensation (47.0%), and burning (46.0%). In addition, patients in these grades

were using eye drops (67%), systemic medications (47%), and had a previous diagnosis of dry eye (63%) at the time of the analysis (Figure 6).

Table 4 Prevalence of different grades of Oxford scores according to pre-existing diagnosis and clinical conditions

Grade	Oxford lissamine green staining score (percentage)				
	0	I	II	III	IV
Ocular diagnosis					
Dry eye	34	34	43	48	57
Chronic blepharitis	14	18	19	15	3
Ocular allergy	14	15	18	11	9
Previous ocular surgery ^a	13	14	13	18	18
Glaucoma	5	11	14	12	10
Contact lens wearer	9	7	10	8	7
VII nerve palsy	3	1	2	6	1
Herpes zoster ophthalmicus	1	0	2	2	4
Systemic diseases					
Diabetes mellitus	6	11	11	16	22
Sjögren's syndrome	0	2	8	10	31
Autoimmune disease (SLE, RA)	0	1	4	10	16
Rosacea	2	5	3	7	6
Other conditions					
Digital screen user	34	27	18	11	4
Topical treatment (drops)	32	44	54	64	80
Preserved drops	22	36	44	49	63
Preservative-free drops	5	4	5	10	12
Systemic medications	11	20	31	40	60

Notes: ^aKeratorefractive or cataract surgery. The blue shading indicates larger proportion of eyes affected. Bold values indicate the two highest proportions of eyes affected.

Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

A total of 1,135 (41.6%) patients were already using eye drops at the time of the survey; 88% used preserved drops and only 12% used unpreserved eye drops. As many as 80% of patients with Oxford grade IV staining score were on lubricant eye drops, 63% of them with preserved formulations and only 12% with preservative-free lubricant eye drops. Overall, there was a higher proportion of patients with positive corneal fluorescein staining using preserved eye drops ($P=0.002$). Also, there was a significantly higher rate of ocular surface damage in patients using preserved eye drops for more extended periods of time ($P=0.046$) (Figure 7).

The great majority of patients, between 70% and 93%, using systemic medications showed positive fluorescein staining ($P=0.0024$). Patients reported using mainly hypoglycemic and anti-hypertensive drugs (data not shown).

Finally, 76% of patients with a history of cataract surgery and 77% with refractive surgery had a positive corneal fluorescein staining ($P=0.754$).

Discussion

Studies searching for risk factors for ocular surface damage related to DED are important because they provide specific information with regard to the epidemiologic features of a given population based on geographic, environmental, demographic, socio-economic, and cultural aspects.^{2,19,20} The population analyzed in the present study is a representative sample of different geographic regions from Mexico, a country

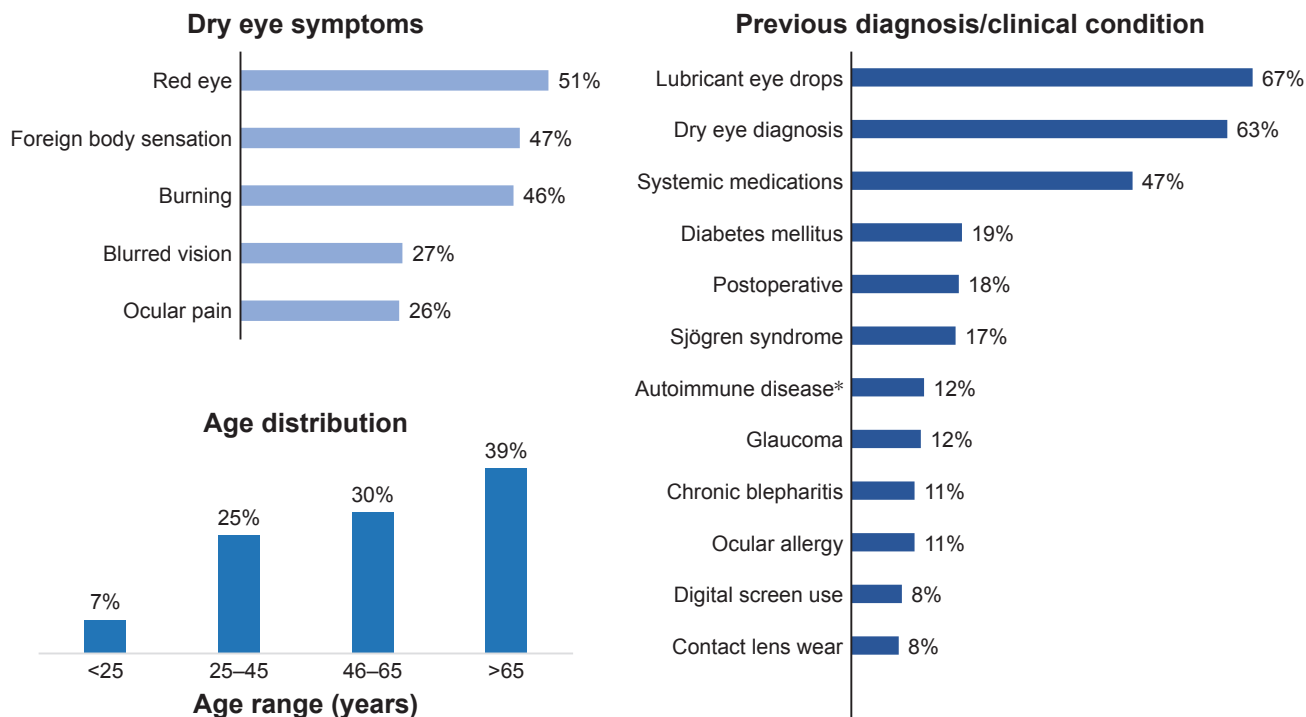


Figure 6 Profile of patients with severe ocular surface damage corresponding to grades III and IV of the Oxford lissamine green staining scheme.

Note: *RA/SLE.

Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

with multivariate climates and socio-economic and cultural characteristics. The majority of patients in the present study live and work part- or full-time outside in densely populated urban areas like Mexico City, Guadalajara, and Monterrey,

which are also ranked among the ten most polluted cities in the country with high particulate matter-10 μm (PM₁₀) indexes (Table 1). Several studies have demonstrated that environmental factors influence the prevalence and play

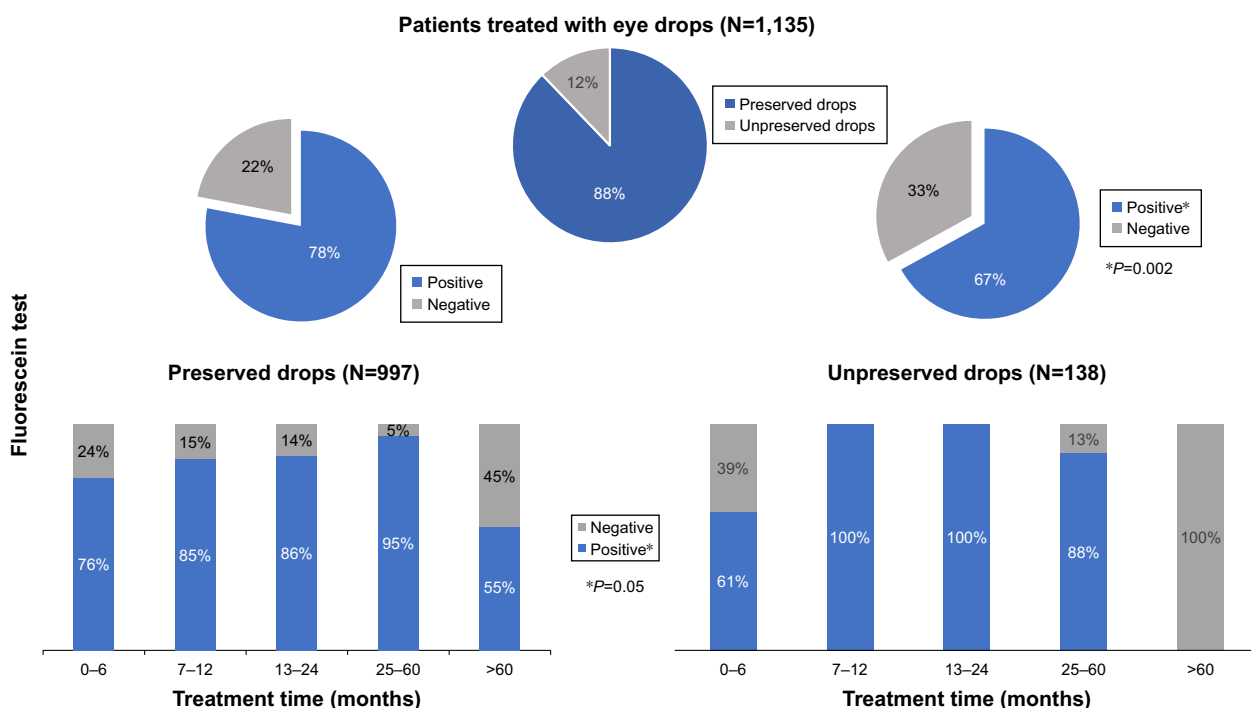


Figure 7 Comparison of positive corneal fluorescein staining between patients previously treated with preserved and preservative-free eye drops over time.

an important role in the pathogenesis of DED.²¹ In fact, a whole new concept of environmental dry eye disease has gained recognition as a new clinical subtype of dry eye.²² High air pollution from automobile exhausts and industrial emissions in densely populated cities produce ocular surface damage increasing the incidence of ocular discomfort and tear film instability.^{23,24} Moreover, most of the urban areas where our study was performed are located at a very high altitude (>1,500 m above sea level), and it has been shown that high-altitude exposure contributes significantly to tear film instability and TBUT reduction.^{25–27} On the other hand, at least one-third of our patients work in closed environments like offices, health care facilities, and poorly ventilated confinements with high variations in airflow and humidity. Also, many of them expend most of their time in front of a computer or other digital screen displays and are exposed to other internal toxic elements like high carbon dioxide concentrations, air conditioning, carpeting, and other furniture materials which may contribute to their dry eye symptoms and ocular surface damage.^{28–30}

Like in other DED population-based reports, around one-third of responders in the present study complained of dry eye symptoms.^{11,19,31} Also, more than 70% of those evaluated had a positive fluorescein test, and this prevalence increased proportionally to the number of reasons for consultation recorded for each patient. This finding implies that more than two-thirds of the population surveyed, complaining of one or more symptoms of dry eye, had some degree of ocular surface damage. Moreover, superficial punctate keratitis was found in 68% of these patients, expressed as significantly positive corneal fluorescein staining in at least one eye, with a higher proportion in women at older ages (Figures 3 and 4). This significant ocular surface damage reported in our patients is similar to what previous epidemiologic reports on DED have encountered.^{9,11,13} Additionally, the most commonly reported diagnoses in the present study, namely, dry eye, chronic blepharitis, and ocular allergy, are also among the most common causes of DED reported worldwide.^{16,32,33} Not surprisingly, dry eye, Sjögren's syndrome, and glaucoma were the three diagnoses recorded from our patients that showed a higher correlation with significant corneal fluorescein staining (Figure 1). Sjögren's syndrome, one of the most severe forms of DED, has been shown to cause significant damage to the ocular surface, reflected by higher Sjögren's International Collaborative Clinical Alliance (SICCA) (≥ 5 points) and Oxford (grades III–IV) scores.^{17,34,35} On the other hand, glaucoma and topical anti-glaucoma therapy have more recently been mentioned as frequent and serious causes

of ocular surface disease.^{36–38} The number of anti-glaucoma medications and the frequency of drops administered per day are known to increase the ocular surface damage in these patients.^{36,39,40}

In regard to treatment, the great majority of patients with severe ocular surface damage (Oxford grade IV staining score) were already on long-term lubricant eye drops at the time of the survey; 63% of them were using preserved formulations as opposed to only 16% who were using preservative-free drops. Knowing the potential and cumulative toxic effect of detergent preservatives like benzalkonium chloride present in many topical eye formulations, it was not surprising to find a significantly higher rate of ocular surface damage in patients using preserved lubricant eye drops for longer periods of time⁴¹ (Figure 7). Hypoglycemic and anti-hypertension systemic medications were also found to have a significant correlation with ocular surface damage related to DED. In general, different types of systemic drugs may exacerbate dry eye signs and symptoms, particularly anti-histamines, anti-depressants, anti-anxiolytics, and diuretic drugs.⁴²

Conclusion

Patients with DED are exposed to many different factors that contribute in different ways to their signs and symptoms. In the present study, geographic and adverse environmental factors may have a significant contribution to the high prevalence of ocular surface damage that was found.

The present report shows that the profile of Mexican patients with significant ocular surface damage related to DED includes older age women complaining of red eye, foreign body sensation, and burning. Previous or known diagnoses of dry eye, Sjögren's syndrome, or glaucoma were also risk factors for developing significant ocular surface damage, along with long-term use of topical treatment with preserved eyes drops and systemic medications.

The limitations of population-based studies evaluating DED and its consequences are based on differences in ethnic, geographic, cultural, and socio-economic aspects, and also on the methodology and clinical characteristics included in the study. Therefore, comparative analysis is difficult and limited. In the present report, we did not explore all risk factors for DED due to the nature of the survey and the way it was designed. For those reasons, detailed and extensive screening was not possible. However, the data obtained in the present survey are of value for the identification of potential risk factors for significant ocular surface damage related to dry eye in Mexican patients.

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Disclosure

The authors report no conflicts of interest in this work.

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